Renal effects of exogenous and endogenous dopamine

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SUMMARY AND CONCLUSIONS.

Dopamine is generally considered as a valuable drug in clinical medicine. The expression "renal dose" of dopamine is often used and known to most physicians. This illustrates not only that they are familiar with the idea of a specific dose range to obtain the desired effects but also the value attributed to these renal effects of the drug. Infusion of dopamine results in an increase in renal blood flow, glomerular filtration and sodium excretion. This is the result of stimulation of specific dopamine receptors. At higher dopamine infusion rates, renal blood flow and glomerular filtration fall again which is usually ascribed to stimulation of adrenoceptors, resulting in renal vasoconstriction. The link between the effects of dopamine and stimulation of specific receptors has been based on pharmacological studies using dopamine and adrenergic receptor agonists and antagonists.

The facts that dopamine is present in the kidney and in even much larger amounts in urine, that specific dopamine receptors exist within the kidney, and that stimulation of these receptors elicits such marked renal effects, makes it attractive to suppose an important physiological role for this third naturally occurring catecholamine in the kidney.

This thesis describes the renal effects of some dopamine and alpha-adrenergic receptor antagonists before and during infusion of dopamine in various doses in normal man and in patients with renal disease. An attempt is made to draw some conclusions on the physiological and possibly pathophysiological role of endogenous dopamine.

Chapter 1 provides an extensive review of the renal effects of dopamine. In the historical section the importance of adequate dose-finding studies is highlighted. After a description of the various receptors which may be stimulated by dopamine, the renal effects of exogenous and of endogenous dopamine are discussed separately. Several mechanisms may be responsible for dopamine-induced natriuresis. The renal vasodilation per se has often been considered as the main factor; however, recent evidence supports the assumption that direct tubular effects of dopamine are at least complementary. The inhibition of aldosterone release by dopamine may also contribute to the natriuretic effect of dopamine. A pathophysiological role of defective dopamine generation in essential hypertension and some oedematous disorders like congestive heart failure has been suggested but the available evidence does not allow firm conclusions in this respect. This does not exclude a possibly valuable role in the treatment of such diseases for selective and orally active dopamine agonists which have recently become available for clinical use.

Chapter 2 states the purpose of the studies which were performed in normal volunteers and in patients with renal disease and moderately impaired renal function. A general description of the study population, the study protocols and the methods is given.

Chapter 3 describes the renal effects of dopamine dose-response curves in normal volunteers and patients with renal disease. In earlier studies of Beukhof et al in patients

with IgA-glomerulopathy, and of ter Wee et al in a larger group of patients with various renal diseases, an impaired response of ERPF and GFR to infusion of a fixed dose of 1.5-2.0 μg/kg/min dopamine compared to normal volunteers was found. Below a base-line GFR of 73 ml/min/1.73 m^2 dopamine did not change ERPF or GFR; above this level the dopamine-induced rise in ERPF and GFR was larger with increasing base-line GFR. Even when the base-line GFR of a patient with renal disease was within the normal range his response to the fixed dose of dopamine was impaired compared to a healthy control subject. It was concluded that in patients with renal disease, nephron loss could be compensated for by a progressive utilization of the so called reserve filtration capacity. The possibility was proposed that an increase in endogenous renal dopamine was involved in this recruitment of reserve filtration capacity: renal vasodilation resulting from stimulated renal dopamine generation compensates for a fall in renal blood flow after nephron loss in a patient with renal disease. If such a hypothesis is true, the validity of a fixed-dose dopamine infusion for testing reserve filtration capacity can even be questioned: an impaired renal haemodynamic response cannot be assumed to represent only a fall in recruitable renal vasodilatory potential but may also reflect the competition of exogenous dopamine and stimulated endogenous dopamine for binding to dopamine receptors which induce renal vasodilation.

We decided to test the hypothesis of enhanced renal dopamine generation in patients with renal disease both by studying the effects of dopamine antagonists and by performing dose-response studies with exogenous dopamine. If renal disease would be associated with an increased renal dopamine generation, an enhanced sensitivity to dopamine antagonists, revealed by a renal vasoconstrictory response and possibly a fall in sodium excretion, should be found. A flattened dose-response curve, not only absolutely but also percentually, for exogenous dopamine would form another, albeit less persuasive argument for enhanced renal dopamine generation.

The results in chapter 3 show that for the renal haemodynamic parameters in patients with renal disease compared to healthy volunteers, an impaired percentual response was indeed found. In the normal volunteers a marked dose-dependent renal vasodilatory response was established which was already evident at a dose of 0.25 μg/kg/min, and reached its maximum at a dose of 4 μg/kg/min. The increase in GFR was modest. The reduction in the renal vasodilatory response in the patients with renal disease was found for the complete dose-range of dopamine. However, the natriuretic response to dopamine did not differ between the patients and the healthy volunteers. This casts some doubt on the hypothesis of an enhanced renal dopamine generation, although a local vascular increase in dopamine generation cannot be excluded. The fact that patients with renal disease had an impaired renal vasodilatory but a conserved natriuretic response to dopamine, formed our first argument for the assumption that the dopamine-induced natriuresis does not depend on renal vasodilation. As discussed above, direct tubular effects or an aldosterone-inhibiting action of dopamine might be other factors involved in the increase in sodium excretion. Additional arguments for a direct tubular action were supplied by the observed changes in the excretions of calcium, γ-glutamyltransferase and β-2-microglobulin, and in the tubular resorption of phosphate.

Further arguments to refute the hypothesis that enhanced endogenous dopamine generation in patients with renal disease is responsible for their impaired renal vasodilatory response to exogenous dopamine were provided by the study described in chapter 4. We examined the effect of the dopamine antagonist metoclopramide on base-line values and dopamine dose-response curves for renal haemodynamics and sodium excretion in healthy volunteers and in patients with renal disease.

Metoclopramide shifted the dopamine dose-response curve for renal vasodilation in the healthy volunteers and may therefore be assumed to act as a dopamine antagonist in the human kidney. Neither in the healthy volunteers nor in the patients with renal disease was any effect on base-line values of ERPF or FF found, thereby undermining the assumption that the impaired renal vasodilatory response in the patients with renal disease is due to enhanced endogenous dopamine generation. However, metoclopramide induced a fall in sodium excretion and a shift of the dopamine dose-response curve for natriuresis. This might represent the contribution of endogenous dopamine to sodium excretion on the one hand and is a second argument for a natriuretic action of dopamine which is independent of its renal vasodilatory effect on the other hand. One might presume that, while the renal effects of exogenous dopamine comprise both renal vasodilation and natriuresis, endogenous dopamine has no influence whatsoever on renal vessels and its only role is in modulating sodium excretion. However the demonstration of dopamine receptors in several renal vessel types and the observation that very high doses of metoclopramide may decrease renal plasma flow argue against such an assumption. The observed changes in the fractional excretions of γ-glutamyltransferase and β-2-microglobulin again support a direct (proximal) tubular effect of dopamine. The observed fall in aldosterone concentration during dopamine infusion and its rise during metoclopramide draw attention to the contributory role of aldosterone in the natriuretic effect of dopamine.

In chapter 5 the effects of another dopamine antagonist, sulpiride, have been examined. For metoclopramide other human studies had suggested dopamine antagonist activity at the renal level; for sulpiride comparable evidence from studies in man was scant despite the fact that in animal studies this drug is a very potent antagonist of dopamine-induced renal vasodilation. Therefore, and also because sulpiride in contrast to many other potent or selective dopamine antagonists is clinically available, we started a study of its effect on dopamine-induced renal vasodilation in healthy volunteers. To our surprise no effect whatsoever on the dopamine dose-response curves for ERPF or FF could be found. A fall in sodium excretion at base-line and its impaired response to dopamine infusion was assumed by us to represent a dopamine antagonist action of sulpiride on the natriuretic effects of endogenous and exogenous dopamine, respectively, which made it less likely that the dose of sulpiride had been too low to detect antagonist activity on dopamine-induced renal vasodilation. In the animal studies investigating the effects of sulpiride on dopamine-induced renal vasodilation, pretreatment with alpha-adrenergic antagonists had been used to block the alpha-adrenergic effects of dopamine. As sulpiride is known to possess some alpha-antagonist activity, we discussed the possibility that this might have obscured the

dopamine antagonist activity in our studies. We decided to repeat our sulpiride studies after pretreatment with alpha-blockers. Pending the results of alpha-blocker experiments, we discontinued the sulpiride studies in patients with renal disease of whom three had been investigated sofar. The results of these patients are also mentioned in chapter 5. Meanwhile the contrast between the antinatriuretic effect of sulpiride and the lack of effect on dopamine-induced renal vasodilation formed another argument for a dissociation between dopamine-induced renal vasodilation and natriuresis.

Chapter 6 is devoted to the relation of alpha-adrenergic and dopaminergic renal effects. In the first two parts of this chapter dopamine dose-response curves without and with sulpiride are described after pretreatment with the selective alpha-1-blocker prazosin and the aselective alpha-adrenoceptor antagonist phentolamine, respectively. We conclude that sulpiride does not show any activity as an antagonist of dopamine-induced renal vasodilation in man during pretreatment with either prazosin or phentolamine. The earlier observed fall in sodium excretion is confirmed and again supports a role for endogenous dopamine in maintaining sodium excretion. We cannot explain why this potent antagonist of dopamine-induced renal vasodilation in various animal studies fails to show any such effect in our human experiments. During both forms of pretreatment with an alpha-blocker dopamine lost its natriuretic effect. Therefore we performed a separate study comparing dopamine dose-response curves with and without prazosin pretreatment in which prazosin was found to impair not only the natriuretic but also the renal vasodilatory action of dopamine, although base-line values were not altered by prazosin. A comparable study in patients with renal disease gave somewhat different results: while base-line sodium excretion fell and the patients also exhibited an abolished natriuretic response to dopamine during prazosin pretreatment, base-line values of ERPF, GFR or FF nor their renal vasodilatory response to dopamine were affected by prazosin. Several possibilities to explain this unexpected reduction in the natriuretic response to dopamine are discussed. One of the proposed theories suggests that alpha-blockade results in enhanced endogenous renal dopamine generation. Although this theory covers most of the observations in this study, no other clinical or experimental studies or data on dopamine levels are available to support such a theory which, therefore, remains speculative. Another theory involves the selective effects of the DA_1 dopamine and the alpha-1 adrenoceptor on phospholipase-C and its relation to sodium excretion. Stimulation of alpha-1 adrenoceptors is a prerequisite for phospholipase activation and might explain why alpha-blockade in our studies abolished a phospholipase-C-mediated natriuretic response to dopamine. In this theory we also propose the blunted response of the ERPF to dopamine infusion during prazosin pretreatment to be a consequence (and not a cause) of the abolished natriuretic response. In fact, a synergistic effect of alpha-1 adrenoceptor and DA_1 dopamine receptor stimulation on phospholipase-C-mediated sodium excretion might explain the disproportionate rise in sodium excretion during infusion of dopamine in doses at which ERPF starts to fall due to the vasoconstrictory effect of alpha-adrenergic stimulation. The present studies also examined for the first time the acute (within one day of starting the drug) effects of prazosin on renal haemodynamics and sodium

excretion. The lack of effect on these parameters agrees with the results from studies on the renal effects of chronic prazosin treatment.

Finally, in chapter 7 we investigated plasma and urine free dopamine levels under the study conditions which had been used in the previous chapters. No change in these levels could be detected under our base-line study conditions which included moderate hydration in volunteers which were in a supine position (except for voiding), and repeated venapuncture. No evidence for a possible circadian rhythm during our study period was found. Infusion of dopamine at doses of 0.25 and 0.5 µg/kg/min resulted in huge increases in plasma dopamine levels while urine dopamine rose to levels slightly above the physiological range. At higher infusion rates which were associated with observable renal effects in our earlier studies, a sharp increase in urine dopamine was observed while that of plasma dopamine became less outspoken. We concluded that the observation made under physiological circumstances that there is a far better correlation between the assumed renal effects of endogenous dopamine and urine dopamine than plasma dopamine, is also valid for the renal effects of exogenous dopamine. Phentolamine but not prazosin administration was associated with a small rise in plasma dopamine. Urine dopamine was changed by neither of them, a finding which undermines the theory of an increase in endogenous renal dopamine during alpha-blockade which had been proposed in chapter 6. When our preliminary data on dopamine levels in patients with renal disease are confirmed, including the low urine dopamine excretion (even when corrected for a normal GFR), this will form another objection to our earlier formulated hypothesis of an enhanced endogenous renal dopamine generation in patients with renal disease.

In conclusion our pharmacological studies have confirmed an impaired renal vasodilatory response in patients with renal disease. However, their natriuretic response to dopamine is conserved. No supportive evidence was found for the assumption that the impaired renal vasodilatory response to dopamine in the patients with renal disease is due to enhanced endogenous dopamine generation. Both in normal volunteers and patients with renal disease, endogenous dopamine seems to have a role in sodium excretion. The dopamine-induced natriuresis does not depend on renal vasodilation but is probably due to direct proximal tubular effects although inhibition of aldosterone secretion may contribute to the natriuretic effect of dopamine. Metoclopramide but not sulpiride was shown to act as an antagonist of dopamine-induced renal vasodilation; both drugs antagonized dopamine-induced natriuresis. Alpha-blockade, both selective alpha-1-adrenergic using prazosin and aselective using phentolamine, abolished dopamine-induced natriuresis by an as yet unknown mechanism.

Studies using selective agonists and antagonists for DA_1 and DA_2 dopamine receptors may allow a better definition of the contribution of various receptors to the renal effects of endogenous and exogenous dopamine.